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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/444,994	05/19/1995	PETER PALESE	6923-054	8839

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EXAMINER
PARKIN, JEFFREY S

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Application No.	Applicant(s)
08/444,994	PALESE ET AL.
Examiner	**Art Unit**
Jeffrey S. Parkin, Ph.D.	1648

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[·] Responsive to communication(s) filed on *20 December 2001* .

2a)[·] This action is **FINAL**. 2b)[ ] This action is non-final

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[·] Claim(s) *2-8,11,12,14-17 and 57-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *2-8,11,12,14-17 and 57-74* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[x] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other: .

Response to Amendment

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the communication received 20 December, 2001, wherein claims 1, 9, 10, 13, and 46-56 were canceled without prejudice or disclaimer, claims 2, 4-8, 11, 12, 14, and 15 amended, and new claims 57-74 submitted. Claims 2, 4-8, 11, 12, 14, 15, and 57-74 are currently under examination.

Claim Objections

2. The previous objection to claims 1, 11, 15, and 48 for failing to reflect the restriction requirement is hereby withdrawn in response to Applicants' amendment.

35 U.S.C. § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The previous rejection of claims 1-8 and 11-17 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is hereby withdrawn in response to Applicants' amendment.

5. Claims 2-6, 11, 12, 14-17, and 37-44 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed toward methods for identifying compounds that inhibit interactions between the influenza virus nucleoprotein, or fragments thereof, and a host cell protein, or fragments thereof. Claims employing a nucleoprotein fusion protein, and fragments thereof, are also presented. The specification describes the utilization of a yeast interactive trap system to identify putative factors that bind to each other. A HeLa cDNA expression library was created and transformed into yeast cells comprising a reporter construct and lexA-NP fusion protein. If a particular colony expresses a protein that binds to the NP protein, the reporter construct is activated. This system enables the investigator to isolate the cDNA and further characterize the interacting protein. The disclosure describes the identification of six putative NP interacting proteins designated NPI-1-6. The nucleotide and amino acid sequences of two of these proteins (NPI-1 and -2) were ascertained and it was noted that the proteins are homologous to SAP1 and hnRNP C. The remaining four sequences were not characterized to any significant extent. Appropriately drafted claim language directed toward the full-length NP protein and the six NPI proteins identified would be acceptable (i.e., An assay for identifying a substance ... (a) contacting the influenza virus nucleoprotein (NP) with an NP interacting protein selected from the group consisting of NPI-1, -2, -3, -4, -5, and -6, ...).

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that

several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide sufficient guidance pertaining to those host cell proteins that are capable of binding specifically to the influenza virus NP. The screening assay relied upon is unpredictable. Accordingly, the skilled artisan can not reasonably predict which host cell proteins will function in the claimed assay. While a small number of HeLa cell proteins were identified that bind to the NP, these proteins do not appear to share any common structural features. Moreover, it is not readily manifest that these binding interactions are critical to the viral lifecycle. The mere finding that two proteins interact with one another does not mean that the binding interaction is meaningful in the context of a viral infection. It needs to be demonstrated that the binding interactions are specific and relevant to the viral lifecycle.

2) The disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating these specific binding interactions. In the absence of such information, the skilled artisan can not reasonably predict which peptide fragments from either the viral or cellular protein should be employed in the screening assay. While it is noted that a single NP1-1 fragment corresponding to amino acids 262-527 functioned in the recited assay, this finding fails to provide any guidance pertaining to suitable portions of the NP protein that will function in the assay. It is also insufficient to enable the breadth of the claim

language as it applies to other NPI protein fragments. The claims encompass peptides as small as a few amino acids to nearly full-length proteins. Absent a showing of those regions that are critical for binding activity, the skilled artisan is only being extended an undue invitation to further experimentation. Moreover, the NPI peptides identified to date fail to display any genetic relatedness. Thus, even if the applicants had carefully mapped the molecular determinants modulating the interactions of one NPI (which clearly has not been performed), it is not clear that these findings could even be extended to other NPIs due to their genetic unrelatedness.

3) The art is unpredictable and fails to provide any guidance pertaining to those host cell proteins, and fragments thereof, as well as fragments of NP, that will function in the recited assay. The disclosure fails to provide a predictable screening method that will result in the identification of related proteins. The yeast trap system employed only identified six putative NPI proteins. To date, none of these proteins share any genetic relatedness. Thus, when the skilled artisan practices the claimed invention, they can not predict which proteins will function in the desired manner. Moreover, even if a putative NPI is identified, it does not mean that the binding interaction is critical for the viral lifecycle. For instance, due to non-specific binding interactions it may appear that two proteins bind to and interact with each other in the *in vitro* screening assay employed. However, this system lacks all the components required for a productive viral infection *in vivo*. Thus, the skilled artisan can not ascertain the importance of this binding interaction without further undue experimentation.

4) The disclosure fails to provide a sufficient number of working embodiments. The specification only describes the identification of six apparently unrelated molecules that interact with the influenza virus NP. Two of these molecules were subjected to

further characterization wherein it was noted that they are genetically unrelated. It is not readily manifest if any of these binding interactions are critical *in vivo* for viral replication. The disclosure also fails to provide working embodiments involving a reasonable number of NP or NPI peptidic fragments.

5) Finally, the claims are of excessive breadth and are not fully supported by the disclosure. As noted *supra*, the claims encompass any host protein and fragments thereof, as well as, fragments of the NP protein. However, the screening assay employed has only identified a small number of putative NPI proteins. The disclosure fails to provide any guidance pertaining to the ability of any given peptidic fragment to function in the assay and the importance of these binding interactions on viral replication.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Applicants traverse and argue that sufficient guidance is provided in the specification to enable the full breadth of the claimed invention. Applicants contend that the identification of six NPIs is sufficient to enable the full breadth of the claimed invention. It was further argued that sufficient guidance pertaining to suitable fragments was also provided. These arguments are not deemed to be persuasive for the reasons immediately set forth *supra*.

Finality of Office Action

4. Applicants' amendment necessitated any and all new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS**

FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Correspondence

7. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 O.G. 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 305-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

8. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1646

31 October, 2002

JAMES HOUSEL 11/4/02
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600